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Biochemical Validation of Self-Reported Exposure to Environmental Tobacco Smoke[1]

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Biochemical validation of reported exposure to environmental tobacco smoke (ETS) lends credibility to epidemiological studies investigating the association of passive inhalation of smoke to respiratory disease or lung cancer. In the current study, a series of questions regarding ETS exposure was self-administered to nonsmokers and self-reported intensity of exposure was compared with cotinine levels in urine samples obtained on site. The target population of this study was a group of municipal workers who reported exposure in a domestic setting and/or in the workplace. When asked if they were exposed to ETS on social occasions, both males and females who responded positively had higher urinary cotinine levels ($P < 0.02$) than those who gave a negative response. Mean urinary cotinine concentrations were found to be elevated in both men and women who reported that they lived with a smoker. Cotinine levels in the urine of those reporting exposure were over twice as high as those in the urine of respondents who denied having been exposed. ETS exposure in the home was the greatest contributor to increased urinary cotinine levels in both men and women. Among individuals who were exposed at work only, the reported degree of exposure agreed well with the mean urinary cotinine values. Those findings emphasize that the validation of exposure status with a biomarker is an essential prerequisite for epidemiological studies investigating passive smoking. © 1989 Academic Press, Inc.

INTRODUCTION

Nonsmokers are exposed to environmental tobacco smoke (ETS) in a variety of places including home, workplace, and social surroundings (U.S. Department of Health and Human Services, 1986; National Research Council, 1986). The degree of such exposure is a function of the time an individual spends in each setting and the concentration of tobacco-related air pollutants in that environment (National Research Council, 1986). Chronic exposure to ETS has been implicated as a factor in the induction of bronchitis, pneumonia, and infections of the lower respiratory tract in both adults and children (Wald *et al.*, 1986; Schenker *et al.*, 1983; Ferris *et al.*, 1985). Some evidence suggests an association between increased risk for lung cancer and exposure to ETS (National Research Council, 1986; Wald *et al.*, 1986; Hirayama, 1984). While further studies are necessary to establish the relative risk of lung cancer from ETS exposure, considerable research has been conducted on measuring the exposures of nonsmokers to ambient tobacco smoke

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constituents (National Research Council, 1986; Russell and Feyerabend, 1975; Sepkovic *et al.*, 1986; Jarvis *et al.*, 1984; Husgafvel-Pursianinen *et al.*, 1987).

Cotinine, a major metabolite of nicotine, is currently the best marker of tobacco exposure through active inhalation (Haley *et al.*, 1983) and passive smoke exposure (Russell and Feyerabend, 1975). The determination of urinary nicotine and cotinine relative to creatinine has been applied to evaluations of controlled exposures to ETS (Hoffmann *et al.*, 1987; Axelrad *et al.*, 1987) as well as to self-reported free-living exposures (Sepkovic *et al.*, 1988; Greenberg *et al.*, 1984).

The current study was designed to evaluate whether self-reported ETS exposure and urinary cotinine levels in a group of employed nonsmokers would correlate especially with regard to the intensity of exposure that was perceived. Furthermore, the study purported to examine how urinary cotinine levels reflect the uptake of ETS constituents from various sources. The population in this study was composed of a group of municipal workers, some of whom reported exposure to ETS at home and/or in the workplace. Questionnaire data and urinary cotinine levels were evaluated to determine mean levels by source of exposure and relative intensity of exposure according to self-report.

METHOD

The study population consisted of 148 men (mean age 38.7 ± 0.9 years) and 112 women (mean age 35.3 ± 1.1 years). Thirty-five subjects chose not to indicate their sex or age in the questionnaire (see Table 1). The Dallas Wellness Association (Dallas, Texas) established a site for the conduct of this study at a health fair for city employees. As prospective volunteers visited the site, they were asked about their smoking status. If they reported to be nonsmokers, they self-administered a questionnaire on ETS exposure. Urine samples were obtained on-site following completion of the questionnaire.

Questionnaire data included age, sex, occupation, and previous smoking history, if any. Specific questions on ETS exposure in the home, workplace, social circumstances, and transportation were asked and self-reported perception of exposure in each situation was rated using a subjective index where 0 equaled no exposure and 4 indicated heavy ETS exposure.

Cotinine in urine was determined by radioimmunoassay after the method of

TABLE 1
DESCRIPTIVE VARIABLES OF THE DALLAS MUNICIPAL WORKER POPULATION

	n	% of population	Urinary creatinine (mg/ml)	Urinary cotinine (ng/ml)	Urinary cotinine (ng/mg creatinine)	Age (years)
Men	148	49	1.62 ± 0.07	9.2 ± 0.8	6.2 ± 0.5[a]	38.7 ± 0.9
Women	112	37	1.45 ± 0.07[b]	11.0 ± 1.3	8.0 ± 0.8[b]	35.3 ± 1.1
Unknown	35	12	1.76 ± 0.15	10.6 ± 1.1	6.4 ± 0.7	Unknown

[a] Each value is equal to the mean ± the standard error of the mean.
[b] Significantly different from men, $P < 0.05$.

Langone *et al.* (1973). This method uses specific antisera produced by injection of *trans*-4-carboxycotinine bound to albumin in rabbits. The inter- and intraassay variations are 6% with a sensitivity of 1.0 ng/ml. Since urinary cotinine has a biological half-life of 20–39 hr in nonsmokers (Sepkovic *et al.*, 1986; Hoffmann *et al.*, 1987; Haley *et al.*, 1988), the values reported reflect exposure that occurred during the recent 3–4 days. The most desirable method of determining cotinine in urine is to collect total urine void over 24 hr. This is impractical for epidemiological studies, so, therefore, an alternative method, normalization using urine creatinine excretion, was employed in the present study. Determination of the excretion ratio of another compound under investigation to that of creatinine is advantageous in some cases. Two examples are vanillylmandelic acid and glucose determinations (Tietz, 1970).

Questionnaire data were statistically assessed using analysis of covariance with the general linear models procedure of the statistical analysis system (SAS, 1985). Least-squares estimates of mean values were obtained and tested for significant differences by Duncan's multirange procedure. Paired *t* tests were also made for comparisons between sexes.

RESULTS

Three hundred and nineteen municipal workers completed the questionnaire. These individuals were invited to participate in the study only after they acknowledged that they were nonsmokers. Of this group, 19 subjects then admitted in writing that they did in fact currently smoke cigarettes. Five individuals stated that they were ex-smokers who had not smoked for the last 6 months to 15 years. However, the urinary cotinine levels for these subgroups ranged from 118 to 3000 ng/mg creatinine. These subjects and those supplying inconsistant answers to the question on current smoking were excluded from the data analysis. Therefore, subjects who did provide data for this study had reported no smoking for at least the past 6 months and had urine cotinine levels of less than 40 ng/mg creatinine. These values are consistent with nonsmoking status.

Characteristics of the volunteers are described in Table 1. The means of urinary cotinine/creatinine were significantly higher in women than in men. These differences are not observed when unnormalized data are being used for comparison. Urinary creatinine levels are different between men and women; thus, cotinine/creatinine ratios may not be appropriate for comparisons between the sexes (Tietz, 1970). When the population was divided according to work environment, it was noted that about 59% of the employees worked indoors, 24% worked outdoors, and 17% worked in a mixed environment. No differences were observed in urinary cotinine levels of these groups. When the population was grouped according to sex, 53% of the men worked indoors and 94% of the women worked in an enclosed environment.

Table 2 provides the subject response to questionnaire data and the mean cotinine levels for each subgroup. As expected, there were no significant differences in urinary cotinine levels that could be related to the occurrence or absence of ETS exposure during childhood. However, this question revealed that 78% of males and 79% of females who answered were exposed to ETS during their

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TABLE 2
COTININE LEVELS AND SELF-REPORTED EXPOSURE

	Urinary cotinine in men (ng/mg creatinine)		Urinary cotinine in women (ng/mg creatinine)	
1. As a child did adults smoke in your presence?				
Yes (n = 116)	6.0 ± 0.5[a]	(n = 89)	8.4 ± 0.9	
No (n = 32)	6.7 ± 1.5	(n = 23)	6.8 ± 1.3	
	(NS)		(NS)	
2. Are you exposed to ETS on social occasions?				
Yes (n = 134)	6.4 ± 0.6	(n = 99)	8.5 ± 0.9	
No (n = 13)	4.7 ± 1.1	(n = 11)	5.2 ± 1.4	
	($P < 0.005$)		($P < 0.025$)	
3. Have you been exposed to ETS on cars, buses, trains?				
Yes (n = 110)	6.6 ± 0.6	(n = 93)	8.5 ± 0.9	
No (n = 37)	5.0 ± 1.0	(n = 17)	6.4 ± 1.8	
	(NS)		(NS)	
4. Is there anyone in your home that smokes in your presence?				
Yes (n = 20)	13.3 ± 2.4	(n = 33)	13.9 ± 1.9	
No (n = 127)	5.1 ± 0.4	(n = 79)	5.6 ± 0.6	
	($P < 0.005$)		($P < 0.005$)	

[a] Each value is equal to the mean ± the standard error of the mean.

childhood years. When asked if they were exposed to ETS on social occasions, 134 men responded positively. The mean cotinine concentrations in urine samples of this group was 6.4 ± 0.6 ng cotinine/mg creatinine, compared to 4.7 ± 1.1 ng cotinine/mg creatinine in the unexposed group. Among women, 99 subjects responded positively to this question. Mean cotinine levels of 8.5 ± 0.9 ng/mg creatinine were observed in urine samples of this group. This mean value was higher ($P < 0.02$) than those women who reported no exposure (5.2 ± 1.4 ng/mg creatinine). The males in this population were exposed to ETS on social occasions for 6.1 ± 1.0 hr/week while the exposure of the women averaged 7.9 ± 1.1 hr/week. When asked if they were exposed to ETS in cars, buses, trains, etc., 110 men and 93 women responded positively, yet no differences were observed between groups.

High urinary cotinine/creatinine concentrations were noted in both men and women who answered affirmatively to the question concerning smoking by others in their presence at home. These results indicate that the nonsmoker who shares living quarters with a smoker has a higher urinary cotinine level than a subject who does not live with a smoker (mean levels were 13.3 ± 2.4 vs 5.1 ± 0.4 ng/mg in men and 13.9 ± 1.9 vs 5.6 ± 0.6 ng/mg in women). Additionally, there were significant differences in the frequency of ETS exposure in the home reported by men (13.5%) and women (29.2%) ($P < 0.002$).

Table 3 describes self-reported ETS exposure in the workplace and gives urine

TABLE 3
SELF-REPORTED ETS EXPOSURE IN THE WORKPLACE AND URINE COTININE LEVELS

Exposure rating	Men: urine cotinine (ng/mg creatinine)	Women: urine cotinine (ng/mg creatinine)
None	4.0 ± 0.6[a] (n = 16)	7.5 ± 1.6 (n = 7)
Slight	6.1 ± 0.8 (n = 70)	7.3 ± 1.2 (n = 55)
Moderate	6.7 ± 1.3[b] (n = 48)	8.7 ± 1.6[c] (n = 32)
Heavy	7.3 ± 1.2[c] (n = 14)	9.4 ± 1.9[b] (n = 18)

[a] Each value is equal to the mean ± SEM.
[b] Significantly different from No Exposure ($P < 0.025$) by paired t test.
[c] Significantly different from No Exposure ($P < 0.05$) by paired t test.

cotinine values for each exposure rating. In both men and women, significantly higher urine cotinine levels were noted in the moderate ($P < 0.05$) and the heavily exposed groups ($P < 0.025$) when compared to nonexposed individuals. However, no positive correlations were noted in either group.

In Fig. 1, mean urinary cotinine concentrations versus self-reported estimates of ETS exposure are plotted for the entire study population. Perceived exposure correlated well with the biomarker. Significant differences were observed between the no exposure group and the moderate ($P < 0.05$) and the heavy exposure group ($P < 0.01$).

Figure 2 illustrates the relative degree of ETS exposure in work and/or home environments. Maximum cotinine concentrations in urine were apparent for home

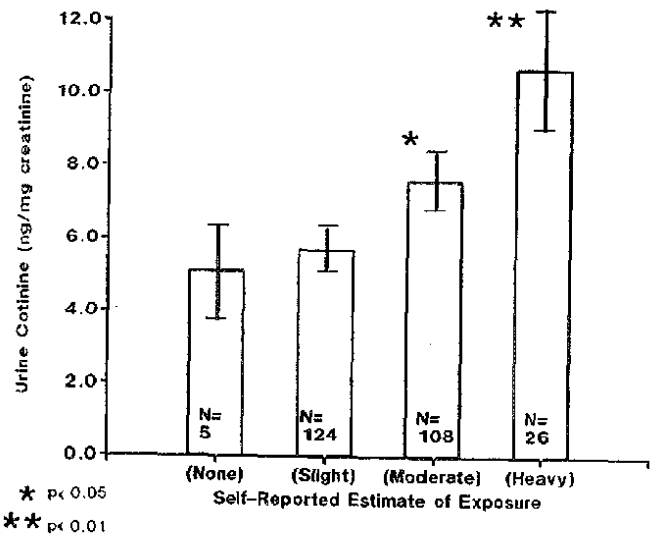

FIG. 1. Mean urinary cotinine concentrations versus self-reported estimated exposure in municipal workers. Self-reported exposure includes social, work, and domestic ETS exposure. Each bar represents the mean (±SEM) of each group. The heavy exposure ($P < 0.01$) and moderate exposure ($P < 0.05$) groups are significantly higher than the no exposure group.

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FIG. 2. Domestic versus work exposure to ETS in male and female municipal workers. The height of each bar is equal to the mean urinary cotinine (±SEM) for each group. Mean urinary cotinine is plotted versus domestic exposure, work exposure, domestic or work exposure, and no exposure, for both men and women.

plus work exposure in both men and women. The greatest ETS exposure, as reflected by urinary cotinine concentrations and self-report, occurred in the home in both men and women.

In Table 4, self-reported ETS exposure in social or occupational and domestic

TABLE 4
SELF-REPORTED ETS EXPOSURE IN VARIOUS ENVIRONMENTS

Home	Work	Social environment	*n*	% of population	Urinary cotinine (ng/mg creatinine)
+	+	+	19	6.3	13.3 ± 2.6[a,b,d,f]
+	+	−	1	0.3	12.2 ± 0
+	−	+	29	9.5	14.7 ± 2.1[c,e,g]
+	−	−	5	1.6	6.8 ± 2.8
−	+	+	30	9.9	5.8 ± 1.0
−	−	+	160	52.6	5.5 ± 1.0
−	+	−	2	0.7	2.4 ± 2.4
−	−	−	16	5.3	4.2 ± 0.8

[a] Each value represents the mean ± SEM.
[b] Significantly different from only home exposure ($P < 0.001$).
[c] Significantly different from only home exposure ($P < 0.025$).
[d] Significantly different from only social exposure ($P < 0.0025$).
[e] Significantly different from only social exposure ($P < 0.0005$).
[f] Significantly different from only work exposure ($P < 0.005$).
[g] Significantly different from only work exposure ($P < 0.001$).

environments are reported and compared with mean values of urinary cotinine concentrations. The urine of those subjects who reported at-home exposure had the highest cotinine levels. These subjects comprised about 18% of the total population. Over one-half of the population (53%) were only exposed during social occasions, but had no exposure at home or at work. The mean of urinary cotinine in this group was 5.5 ± 1.0 ng/mg creatinine.

DISCUSSION

The present study evaluated the reports of ETS exposure of nonsmokers by attempting to provide an index of exposure with urinary cotinine as a biomarker. The results show that people who work or reside with smokers have significantly higher levels of urinary cotinine than those who do not work or live with smokers. The mean urinary cotinine levels observed in this population are in agreement with the findings of other workers (National Research Council, 1986; Wald *et al.*, 1986; Greenberg *et al.*, 1984).

The measurement of urinary cotinine as a direct assessment of ETS exposure is an important tool that can be used to validate self-reported data or questionnaire information. The measurement of cotinine in urine is highly sensitive and specific for tobacco exposure and has been used extensively as an indicator of cigarette consumption and smoking topography. Still, this biomarker provides only an indirect measurement of the potential health risk associated with exposure to ETS. The physicochemical properties of ETS are quite different than those of inhaled mainstream smoke (MS). The carcinogenic potential of ETS, which is indirectly related to the powerful nitrosating agent, nitrogen dioxide, may be greater than that of MS. The appearance of cotinine in the urine of nonsmokers indicates uptake of ETS, but does not necessarily allow us to predict the associated health risks of passive smoking owing to the chemical complexity of ETS and metabolic differences between smokers and nonsmokers (Sepkovic *et al.*, 1986).

Studies that show a correlation between self-report and a specific biomarker for tobacco smoke exposure strengthen epidemiological investigations that causally link passive smoking and respiratory illness. Several studies have shown that never smokers who were spouses of smokers have an increased relative risk for lung cancer (National Research Council, 1986). This increase in risk is also measurable as a function of the duration of exposure to ETS. In contrast, some studies do not support the link between lung cancer and prolonged ETS exposure (Kabat and Wynder, 1984; Garfinkel, 1985). Epidemiological data may be misclassified when self-report or questionnaire data are the only criteria for exposure estimates. This increases the chances of misclassification bias of smokers as nonsmokers (Lee, 1987). The validation of self-report by biomarker enables the researcher to exclude from evaluations those people who say that they are nonsmokers when, in fact, they do smoke. Biochemical validation can also provide a more objective estimate of intensity of current exposure of passive smokers.

The data from this study indicate a positive correlation relationship between self-report and urinary cotinine levels during the adult years. Other researchers, using a passive exposure index in an older outpatient population, reported a similar positive correlation between self-report and cotinine levels in urine (Jarvis

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et al., 1984). By examining the differences which result from exposure at the workplace and at home, this study affords a more accurate assessment of tobacco smoke absorption. In both men and women, the greatest exposure to ETS occurs in the domestic environment.

Overall, the women in our study population had significantly higher levels of cotinine in urine than the men after the results had been normalized against urinary creatinine levels. It is known that men excrete higher levels of creatinine than do women (Tietz, 1970). When urinary cotinine values (ng/ml) were not normalized some of the differences in cotinine levels in men and women were diminished, but a trend toward higher cotinine excretion in women was still observed. This shows that while normalization for creatinine is important for comparisons of urine samples from one person or from a group of men or women, normalization is not helpful for comparisons between sexes. Creatinine excretion is consistent from day to day within the individual. Among healthy children and adults, the expression of nanograms of urinary cotinine per milligram of creatinine reflects the uptake of environmental nicotine from ETS rather well (National Research Council, 1986; Greenberg *et al.*, 1984). Since it is impractical to collect 24-hr urine voids for analyses of tobacco-specific biomarkers in large-scale clinical-epidemiological studies, normalization against creatinine allows cotinine assays in smaller volumes of urine. The additional analyses of course adds cost to the overall study. Therefore, we recommend normalization using creatinine only when a quantitative estimate of tobacco smoke exposure is desired. These additional analyses may not be necessary when simple validation of nonsmoking status in a smoking cessation program is the study endpoint.

In conclusion, the results of the present study indicate there is a positive correlation between urinary cotinine levels and total self-reported perception of ETS exposure. A recent study conducted by Novotny *et al.* (1988) demonstrated that ETS is widely regarded as a health hazard by smokers and nonsmokers alike. About 70% of both smokers and nonsmokers favor policies that restrict ETS exposure at the worksite. In the present study, no national state or local policies to control worksite exposure were in effect. Further studies correlating urine cotinine levels with perceived ETS exposure both before and after the implementation of worksite restrictions are needed to evaluate the effectiveness of these policies. Most exposure to ETS occurs in the home and women more frequently report this exposure than men.

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